

DUPLICATE <sup>W</sup>PALLADIUM CATALYSED C-8 ALLYLATION AND VINYLATION OF  
ADENOSINE, 2'-DEOXYADENOSINE AND 2',3'-DIDEOXYADENOSINE  
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Using a coupling reaction between 8-iodo derivatives of O-TBDMS protected adenosine, 2'-deoxyadenosine, 2',3'-dideoxyadenosine and either vinyltributyltin or allyltributyltin with Pd(PPh<sub>3</sub>)<sub>4</sub> catalysis, the corresponding 8-substituted nucleosides were obtained in excellent yields.

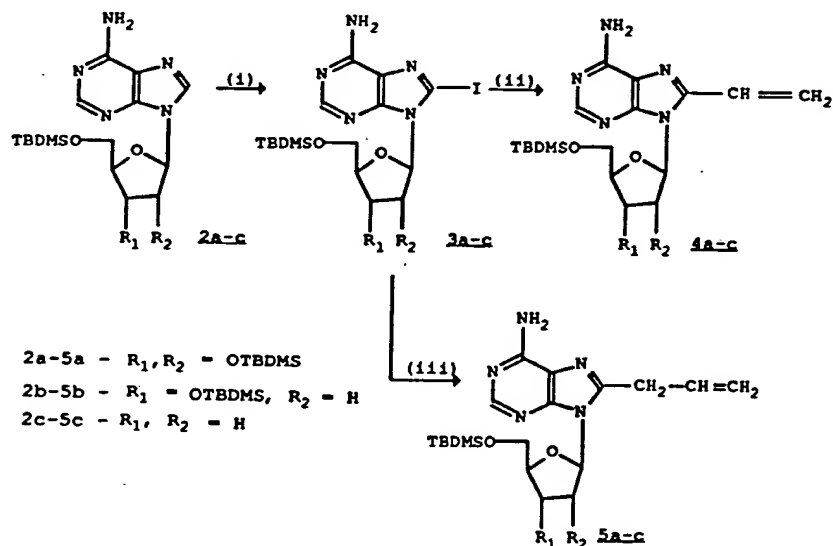
Modified 2'-deoxy and 2',3'-dideoxynucleosides are of interest due to their remarkable biological activity, particularly within the context of anti-viral therapeutic agents<sup>1-3</sup>. Such modified nucleoside analogues can be used for example, in the design of 'antisense' polynucleotides<sup>4,5</sup>, sequence specific DNA cleaving agents<sup>6</sup> and in sequencing DNA<sup>7,8</sup>.

Several methods have been reported for the functionalization<sup>9</sup> of the C-8 position of purine nucleosides. Direct bromination (in a pH controlled buffer) at the C-8 position<sup>10a,b</sup> and subsequent nucleophilic displacement was one of the earliest approaches. Synthetically more satisfactory is the lithiation of the C-8 position of hydroxy protected purine nucleoside with lithium diisopropylamide<sup>11</sup> or n-butyl lithium<sup>12</sup> and reaction with suitable electrophiles. Palladium catalysed coupling of alkynes<sup>13</sup> with 8-bromo purine nucleosides has also been reported. However there exists less precedence in the literature for C-8 functionalization of 2'-deoxy<sup>10b,14</sup> and 2',3'-dideoxy purine nucleosides.

In connection with our interest in functionalized 2'-deoxy and 2',3'-dideoxynucleosides we required C-8 allyl and vinyl analogues as substrates for further transformation. In this communication we report the allylation and vinylation of the C-8 position of t-butyldimethylsilyloxy derivatives of adenosine, 2'-deoxyadenosine and 2',3'-dideoxyadenosine by subjecting the 8-iodo derivatives to Pd catalysed cross coupling with allyl and vinyltributyltin<sup>15</sup> (Table 1).

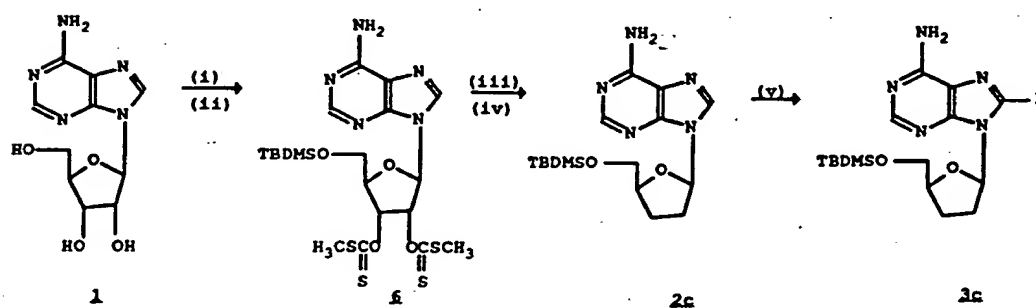
Iodination of the C-8 position using a procedure similar to Miyasaka's for 8-iodo cordycepin<sup>16a</sup>, namely lithiation of the C-8 position of hydroxy protected (with TBDMSCl) nucleoside with LDA at -78°C in THF and quenching with iodine, yielded **3a-c** (Scheme 1). The iodination proceeded with moderate to satisfactory yields<sup>16b</sup> [**3a**-(72%), **3b**-(80%), **3c**-(65%)]. Since protection of the OH groups with TBDMSCl made the nucleosides less polar and hence easier to handle and purify, the protecting groups were retained for the Pd catalysed reactions.

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i) LDA, -78 °C, THF,  $I_2$  (ii) vinyltributyltin,  $Pd(PPh_3)_4$ , DMF, r.t. to 95 °C  
 (iii) allyltributyltin,  $Pd(PPh_3)_4$ , HMPA, r.t. to 145 °C

Scheme 1



i) TBDMSCl, imidazole, DMF (ii) NaOH,  $CS_2$ ,  $CH_3I$ , DMSO (iii)  $Bu_3SnH$ , AIBN, toluene, refl.  
 (iv)  $H_2$ ,  $Pd/C$ ,  $CH_3OH$  (v) LDA, -78 °C, THF,  $I_2$

Scheme 2

Heating 8-iodo adenosine analogues (3a-c) from r.t. to 90-95°C. with vinyltributyltin and 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> in DMF gave the C-8 vinyl nucleosides (4a-c) in high yields after chromatography<sup>17</sup>. Under the same conditions allylation did not take place satisfactorily, yielding a mixture of the desired C-8 allyl nucleoside derivative and C-8 deiodinated nucleoside derivative. This was not totally unexpected because it has been reported that aryl iodides are poor substrates for Pd catalysed allylation with allyltributyltin<sup>18</sup>. Success was achieved using HMPA as the solvent and increasing the temperature to 145°C. Under these conditions the reaction proceeded cleanly, yielding very little of the deiodinated starting material.

Table-1

Synthesis<sup>(17)</sup> of 8-allyl and vinyl t-butyldimethylsilyloxy derivatives of adenosine

Starting Material <sup>(b)</sup>	Product <sup>(b)</sup>	Yield % <sup>(a)</sup>	M.P. <sup>(°C)</sup>
3a	4a	92	179-180
3b	4b	89	112-114
3c	4c	90	148-150
3a	5a	81	138-140
3b	5b	89	132-133
3c	5c	75	84-85

a) Isolated yield after chromatography

b) Characterized by IR, <sup>1</sup>H and <sup>13</sup>C NMR and mass spectra.

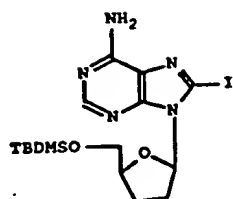
5'-OTBDMS 2',3'-dideoxyadenosine (2c) was prepared following the procedure by Chu et al.<sup>19</sup> (Scheme 2). These workers were unable to reduce the 5'-OTBDMS 2',3'-dideoxyadenosine to the corresponding 5'-OTBDMS 2',3'-dideoxy derivative directly with H<sub>2</sub>/Pd without prior deprotection of the 5'-OTBDMS group<sup>20</sup>. We found that this could be done directly or after pretreatment with Raney Ni<sup>21</sup>. Iodination and coupling of the dideoxy derivative proceeded satisfactorily as well.

In summary we have synthesized C-8 allyl and vinyl derivatives of 2',3',5'-tri OTBDMS adenosine, 3',5'-di OTBDMS 2'-deoxyadenosine and 5'-OTBDMS 2',3'-dideoxyadenosine. This approach should be general for other purine nucleosides as well.

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2c

IBN, toluene, refl.

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b) 8-iodo t-butyltrimethylsilyloxy nucleosides (**3a-c**) were purified through flash chromatography. While **3a** was a crystalline solid (m.p. 171-172.5°C), **3b** and **3c** were obtained as foams. They were directly used in the Pd catalysed reactions, without further recrystallization.
- 17) In a typical vinylation reaction, to a stirred mixture of 8-iodo t-butyltrimethylsilyloxy nucleoside (1eq.) and Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%) in DMF (under Ar), vinyltributyltin (5eq.) was added. The mixture was heated from r.t. to 90-95°C for 30-45 min. TLC showed near quantitative conversion. Workup was done by adding aq. sat. NH<sub>4</sub>Cl, extracting with EtOAc, drying with anhyd. Na<sub>2</sub>SO<sub>4</sub> and evaporating to dryness in vacuo. The crude mixture thus obtained was flash chromatographed on silicagel to yield the pure product, which crystallized either directly or upon cooling to 0°C in hexanes. For allylation a similar procedure and workup was used, except for using HMPA as the solvent and heating from r.t. to 145°C for 30-45 min. TLC again showed high conversion. Though the products **5a** and **5b** readily crystallized in hexanes at 0°C, crystallization of **5c** was not completely satisfactory, tending to remain as a semi-solid or as an oil.
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## Summary:

Oxime  
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